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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	9

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/487,979	Skurkovich et al.
Examiner	**Art Unit**
DeCloux, Amy	1644

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Jun 4, 2001* .

2a) ☐ This action is **FINAL.** 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *42, 45, 46, and 48-50* is/are pending in the application.

4a) Of the above, claim(s) *45 and 48-50* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *42 and 46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15 X Notice of References Cited, PTO-892	18 ☐ Interview Summary, PTO-413, Paper No(s).
16 ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948	19 ☐ Notice of Informal Patent Application, PTO-152
17 X Information Disclosure Statement(s), PTO-1449, Paper No(s). 1	20 ☐ Other

DETAILED ACTION

1. The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Amy DeCloux, Art Unit 1644.

2. The Claims have been renumbered according to Rule 1.126.

Note: A. Claims 1-32 were originally filed.

B. Preliminary Amendment A, (filed 1/20/00), directed the cancellation of claims 33-58 which did not exist. Preliminary Amendment A also directed the addition of claims 59-67. Since there were no claims numbered 33-58, **Claims 59-67 have been renumbered as claims 33-41 according to Rule 1.126.**

C. Preliminary amendment B (filed 11/30/00) stated that Preliminary Amendment A was an error, and directed the cancellation of claims 1-32. Preliminary amendment B also directed the cancellation of claims 59-67 (which have been renumbered as claims 33-41). Preliminary Amendment B also directed **the addition of claims 33-41, which have been renumbered as claims 42-50 according to Rule 1.126.**

D. A restriction was mailed on claims 33-41, (which have been renumbered as claims 42-50).

E. In Amendment C, (filed 6/04/01), Applicants elected Group II , claims 33-35, and 37-38, (renumbered as claims 42-44 and 46-47). Amendment C also directed the cancellation of claims 34-35 and 38 (renumbered as claims 43-44 and 47). Amendment C also directed the amendment of Claim 33 (renumbered as claim 42).

3. Applicant's election without traverse of Group II, claims 33-35, and 37-38, (renumbered as claims 42-44 and 46-47), in Paper No. 7, mailed 5-31-0,1 is acknowledged.

4. Claims 36 and 39-41 (now numbered claims 45 and 48-50) are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Claims 42 and 46 (previously numbered as Claims 33 and 37) are being examined presently.

5. Applicant should amend the first line of the specification to update the status (and relationship) of the priority documents. It is noted that the priority date of the instant application is 12/23/1996 since there is not support in the CIP parent application 08/025,408 filed 2/26/1993 for the instant claims. Applicant is invited to point out support for a method of treating acquired immunodeficiency disease comprising administering a combination of an antibody to gamma interferon, alpha interferon and tumor necrosis factor.

The Preliminary amendment filed on 10-15-99 under 37 CFR 1.312 has been entered-in-part. Most of the amendments to the specification directed by applicant in Preliminary Amendment A (filed 1-20-00) were not entered due to the quantity of amendments and to ambiguousness of the precise locations in the specification which were to be amended.

6. The reference Japanese Journal of Gastroenterology cited in the in the PTO Form 1449 , filed 10-15-99, was not considered, since an English translation was not provided. If applicants wish to have said reference considered, a translation in English should be supplied to the office. Furthermore, it is noted that IDS references "AF, AR, BT, CD and CN" on said PTO Form 149 were not considered since there were no accompanying articles. If applicants wish to have said references considered, a paper copy of each reference should be supplied to the office.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

8. Claim 46 is rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A) Claim 46 is indefinite in the recitation of the term "including" because it is not clear what entities other than those specifically recited are encompassed . It is suggested to replace said term with the word "or".

B) Claims 42 and 46 are indefinite in the recitation in line 3 of claim 42 of the phrase " antibody to tumor necrosis". Perhaps the word "factor" should be inserted after the word "nerosis".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, In such full, clear, concise, and exact terms as to enable any person skilled In the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating Acquired Immunodeficiency Disease (AIDS) comprising administering a combination of an antibody to gamma interferon, (γIFN), an antibody to alpha interferon (αIFN), and an antibody to tumor

necrosis factor alpha, (TNFα), wherein said antibody is a monoclonal antibody, a polyclonal antibody, and biologically active fragments thereof, or allelic or species variants thereof, does not reasonably provide enablement for A) the broader recitation of a method of treating Acquired Immunodeficiency Disease comprising administering an antibody to γIFN, αIFN or TNFα wherein said antibody is any functional equivalent or any derivative thereof, as defined by the instant specification, nor for B) the broader recitation of a method wherein said antibody is directed against any TNF factor other than tumor necrosis factor alpha, (TNFα). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed in the instant claims without an undue amount of experimentation. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of compounds broadly encompassed by the method recited in the instant claim.

The instant specification provides enablement only for a method of treating Acquired Immunodeficiency Disease comprising administering antibody to gamma interferon wherein said antibody is a monoclonal antibody, a polyclonal antibody, and biologically active fragments thereof, or allelic or species variants thereof. However the specification fails to provide guidance as to how to make or use any any functional equivalent or any derivative of the recited antibody, as defined by the instant specification. The instant specification discloses on page 21, that "functional equivalents" of an antibody include any molecule capable of specifically biding to the same antigenic determinant as the antibody, and as such encompasses a wide range of other non-antibody molecules, known and unknown. Additionally, the instant specification discloses on page 21 that "derivative" is intended to include both functional and chemical derivatives including analogs of a molecule and as such encompasses a wide range of non-antibody molecules, known and unknown. Because said claims recite no structural basis for the recited functional equivalent or derivative, it is therefore not clear how to make said equivalent or derivative, and the efficacy of said equivalent or derivative in the claimed method of treating Acquired Immunodeficiency Disease is unclear.

Predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which amino acids in the sequence, if any, are tolerant of modification and which are conserved or less tolerant to modification, and detailed knowledge of the ways in which the product's structure relates to its functional usefulness, as evidenced by the teachings of Abaza et al (J. Of Protein Chemistry,

11(5):433-444, 1992). Abaza et al teach that even a single amino acid difference in an antigen may effect antibody binding by teaching that an amino acid substitution of myoglobin outside the epitope recognized by a monoclonal antibody causes the myoglobin to be unreactive with said antibody, (see entire article, especially the Abstract). Therefore, predicting which functional equivalent or which derivative of the recited antibody, as recited in the instant claims, will retain the desired γIFN, αIFN or TNFα neutralizing effect and therefore will be useful in a method for treating Acquired Immunodeficiency Disease is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Further, it is also noted that TNF alpha and TNF beta are two distinct molecules with distinct properties and expressed in distinct subsets of cells as taught by Figure 7.31 in Janeway et al in Immunobiology 3rd Edition. Given the insufficient guidance provided by the instant specification and by the prior art of the role of administering any TNF molecule, other than TNF alpha, in a method to treat Acquired Immunodeficiency Disease, it would require undue experimentation to predict the effectiveness of any TNF molecule, other than TNF alpha, in the claimed method to treat Acquired Immunodeficiency Disease.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

10. Claims 46 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 46 and dpendent claim 49 recites a method encompassing administering a functional equivalent or derivative of an antibody. The instant disclosure of a "functional equivalent" and "a derivative" of an antibody does not adequately describe the scope of each claimed genus, each of which encompasses a substantial variety of subgenera. Applicant has described "Functional equivalents" of an antibody on page 21, lines 4-6, of the instant specification as any molecule capable of specifically binding to the same antigenic determinant as the antibody, and applicant has described "derivatives" of an antibody on page 21, lines 7-9, of the instant specification to include both functional and chemical derivatives including variants or analogs of a molecule. Since there is no description of the required structural features of said derivatives or functional equivalents, other than that of antibodies and fragments thereof, or of the

conserved regions that would be critical for the IFN-gamma neutralizing features and the TNF neutralizing features of said derivatives or functional equivalents, and given that the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify said derivatives or functional equivalents encompassed, with the exception of antibody fragments, the structure of said derivatives or functional equivalents is not conventional in the art and one of skill in the art would not recognize from the disclosure that applicant was in possession of the genus said derivatives or functional equivalents, the invention encompassing said method is also not adequately described, encompassed by the method of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.)

11. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 42 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uehara et al. (Journal of Interferon Research 13, Supplement 1:PW6-9(Oct. 1993)), (IDS #CP), Skurkovich et al (U.S. Patent No. 4,824,432 (April 989) and Probert et al PNAS 92(24):11294-8 (Nov 1995).

Uehara et al teach a method of administering gamma interferon antibodies into a mouse model of AIDs to treat MAIDs related symptoms (see entire Abstract).

Skurkovich et al teach a method of administering antibodies to alpha interferon for the treatment of AIDS (see entire patent, especially column 2, lines 29-34).

Probert et al teach a method of administering neutralizing antibodies to TNF alpha for the treatment of human CNS disorders including AIDs (see entire article, including the Abstract).

None of the above referenced teach the treatment of AIDS comprising administration of antibodies to gamma interferon, alpha interferon and TNF alpha.

The MPEP teaches that it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Accordingly, one of ordinary skill in the art at the time the invention was made, who wanted to treat a patient with AIDS would have been motivated to make and administer the antibodies to gamma interferon, alpha interferon and TNF alpha taught by Uehara et al., Skurkovich et al., and Probert et al respectively, because Uehara et al., Skurkovich et al., and Probert et al each teach the administration of antibodies to gamma interferon, alpha interferon and TNF alpha, respectively, in a method of treating AIDs, and therefore combining the administration of all three antibodies in a method to treat AIDs flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the teachings of the references and the MPEP 2144.06, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No Claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina

Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Amy DeCloux, Ph.D.
Patent Examiner,
August 27, 2001

David O. Saunders

DAVID SAUNDERS
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